

**3M Medical Department
Corporate Toxicology**

3M Center, Building 0220-02-E-02
St. Paul, MN 55144-1000|
651 733 1773 Fax



October 19, 2004

Dr. Scott A. Masten
Office of Chemical Nomination and Selection
National Institutes of Environmental Health Science/
National Toxicology Program
P.O. Box 12233, MD A3-07
Research Triangle Park
North Carolina 27709
masten@niehs.nih.gov

Re: Request for Comments on Substances Nominated to NTP for Testing

Dear Dr. Masten:

3M Company appreciates the opportunity to provide comments on the August 20, 2004 notice seeking feedback on recent testing recommendations by the National Toxicology Program (NTP), Interagency Committee for Chemical Evaluation and Coordination (69 Federal Register 51691).

Among these recommendations is a proposal for a "class study" on perfluorinated compounds put forward by the United States Environmental Protection Agency (EPA). 3M has long been involved with perfluorinated chemistries and has sponsored extensive research on different substances within this class. We have reviewed the document prepared by EPA in support of its proposal. It is obvious to 3M that the proposal reflects considerable thought and a careful review of the database on perfluorinated compounds.

3M is in general concurrence with the EPA proposal. We support the concept of developing a common set of data on the perfluoroalkyl sulfonates, carboxylates and telomers in order to provide the information necessary to make informed comparisons between these classes of functionalized perfluorinated alkyl compounds. Although a class approach makes sense from a testing and assessment perspective, 3M does not believe that currently available information for these compounds supports a conclusion that the health effects of the class, as defined in the proposal, are additive or cumulative.

The proposal posits that chain length may be an important factor in toxicity, noting that toxicity and persistence appear to increase with increasing chain length. This is generally true for the compounds that have been studied. For example, a series of 3M-sponsored intravenous pharmacokinetic studies conducted in male and female cynomolgus monkeys with C4, C6, and C8 perfluorinated carboxylates and sulfonates supports the hypothesis that as carbon number and/or chain length increases, elimination from the body becomes less efficient.

In addition to carbon number and chain length, other factors may also influence the comparative toxicological profile of compounds within the class. The degree of branching and molecular structure may impart some differences, subtle or otherwise, in pharmacokinetic handling and biochemical interactions. Moreover, major differences observed in elimination of perfluorooctanoate (PFOA) between species and, in some cases, between sexes within species, suggest that differential expression of transporters may play a significant role in elimination and, possibly, uptake, thereby having an influence on accumulation of body burden and expression of toxicity. As designed by NTP, the proposed investigation of the pharmacokinetic

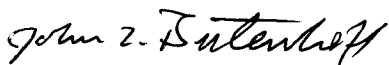
properties of these compounds will provide valuable new insights to these factors as well as to the role of chain length and carbon number. As NTP's study progresses, additional information may be needed to support PBPK models, such as tissue uptake, solubility in biological matrices, and, possibly, saturation of transport mechanisms.

One issue that deserves special comment is the proposal to conduct a chronic cancer bioassay with perfluorooctanoate acid (PFOA), beginning with *in utero* exposure. As the proposal notes, some perfluorinated acids have been shown to be agonists for the peroxisome proliferator activated receptor alpha (PPAR-alpha) and, as such, may produce hepatocellular adenomas and, possibly, other tumor types, in rodents with chronic treatment. The bioassay proposed by EPA is intended to address the potential increased susceptibility of the developing embryo/fetus to tumor formation later in life as a result of *in utero* exposure to PPAR-alpha agonists. This is one of the topics discussed by the EPA Science Advisory Panel that addressed the human relevance of increased hepatocellular adenoma incidence in rodents resulting from a PPAR-alpha agonist-related mode of action.

3M understands why EPA would want to undertake studies to test the hypothesis that *in utero* exposure to PPAR-alpha agonists increases cancer risk with continued exposure into adulthood. However, since the focus of the EPA proposal is to better characterize perfluorinated chemicals as a class, 3M would advise first studying the general pattern of activation of nuclear receptors in the PPAR class for the selected fluorochemicals. In addition, before making a decision to embark on the study proposed for PFOA as a representative of both the class of PPAR-alpha agonist and the proposed class of fluorochemicals, thought should be given to a more broadly focused study to address the basic hypothesis that *in utero* exposure to PPAR-alpha agonists in rodents, in general, may increase susceptibility to tumor formation in adult life following chronic lifetime administration. Use of a non-responsive species or a PPAR-alpha null (genetically-transformed knock-out) model as well as the classic potent PPAR-alpha agonist, WY-14643, would improve the quality of this study by including a non-perfluorinated acid and a non-responsive (to PPAR-alpha agonists) species. Biomarkers of PPAR-alpha response should be followed, even in the PPAR-alpha knockout. These would include increases in hepatic peroxisomes and palmitoyl CoA oxidase activity.

Finally, 3M wishes to offer assistance to NTP on the difficult and time-consuming study startup issues that NTP may face. These include analytical method development and a broad understanding of the chemistries formerly produced by 3M. Pharmacokinetic data needs to be augmented by mechanistic and other basic biological interaction information in order to be put in context and support a sound overall risk assessment. 3M plans to continue its efforts in this area in parallel with the NTP program and would invite a collaborative interaction. In summary, 3M believes that the proposal is sound and offers its support.

Respectfully,



John L. Butenhoff, Ph.D., CIH, DABT
Corporate Scientist

cc: Dr. Oscar Hernandez, USEPA, OPPT, RAD
Dr. Jennifer Seed, USEPA, OPPT, RAD